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Recent Advances in Organocatalytic Glycosylations

Ryan Williams^[a] and M. Carmen Galan^{*[a]}

Dedication ((optional))

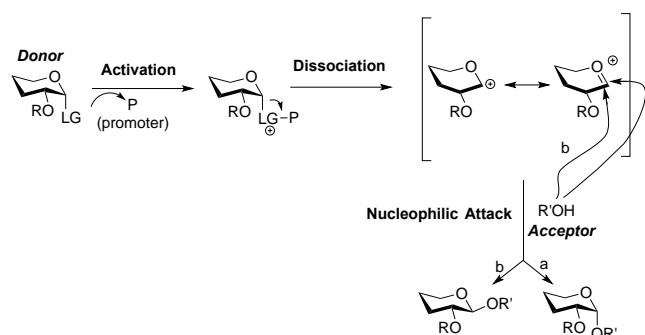
Abstract: Carbohydrates play a pivotal role in biological systems and present an opportunity to develop potent carbohydrate derived therapeutics and diagnostic tools for the treatment and detection of disease. To better comprehend the biological functions of carbohydrates, access to pure and structurally defined oligosaccharides is needed. Oligosaccharides are commonly synthesized by chemical means, however, despite progress in glycosylation chemistry, the efficient and stereoselective formation of glycosidic bonds by mild, non-toxic and low-cost methods remains a challenge. Organocatalysis is an exciting field that utilizes small organic molecules to effect chemical transformation where traditionally transition metal catalysis would be required. This microreview presents recent advances in the application of organocatalysis to carbohydrate chemistry and in particular to the stereoselective synthesis of oligosaccharides.

1. Introduction

Carbohydrates are the most abundant class of natural products on Earth, exhibiting tremendous structural diversity and function.^[1] Complex oligosaccharides have been shown to be an intrinsic component of numerous biological processes, including cell signaling, embryogenesis, neural development, pathogen recognition, inflammation, innate immune responses and cancer. These myriad roles have lead to their use as probes for biological research, as key compounds for drug and vaccine development and in the development of diagnostic tools.^[2] In order to study the function of carbohydrates in detail, it is necessary to have access to sufficient quantities of pure and structurally well-defined oligosaccharides. Enzymatic or chemo-enzymatic approaches to assemble oligosaccharides offer great promise.^[3] The method generally relies on the use of carbohydrate processing enzymes (e.g. glycosidases, glycosyltransferases or glycosynthases) to catalyze the glycosylation reaction with exquisite regio- and stereocontrol. However, these enzymes generally suffer from poor substrate promiscuity, access to the enzymes is limited as the proteins can be challenging to express, they are expensive to employ on scale and only a handful are currently commercially available.^[4] On the other hand, chemical oligosaccharide synthesis can be used to produce glycosides in larger quantities and also offers unparalleled flexibility in terms of choice of coupling partners and reagents, however lack of regio- and more critically stereocontrol during the formation of the glycosidic bond still presents a significant challenge. In spite of this, excellent progress towards the chemical preparation of complex

oligosaccharides has been achieved, with many elegant syntheses having been reported in recent years.^[4] However, to date, no universal glycosylation protocol exists that provides consistently high levels of stereoselectivity. Hence, there is still a need for more sophisticated protocols for glycosylation in order to advance our understanding of carbohydrate function.

Generally, to effect a glycosylation, a glycosyl donor must be functionalized, the anomeric leaving group activated using a promoter in stoichiometric or catalytic amounts and reacted with a partially protected nucleophile acceptor. There many considerations to take into account when discussing the glycosylation mechanism and a clear delineation between S_N1 and S_N2 nucleophilic substitution reactions is difficult to draw.^[5] As depicted in **Scheme 1**, it is generally assumed that a unimolecular S_N1 mechanism is operational under most reactions conditions. To that end, promoter activation of the leaving group forms a reversible or irreversible donor–promoter complex, depending on the system, which leads to the ionization of the glycosyl donor to form an oxacarbenium ion, typically considered an irreversible act, and the rate limiting-step in the reaction. This is then followed by nucleophilic attack by the glycosyl acceptor; and proton transfer (not shown) to give the glycoside product. Recently, the team of Bleriot, Thibaudeau and Jimenez-Barbero^[6] were able to generate and stabilize, for the first time, the glycosylation derived from peracetylated 2-deoxy and 2-bromoglucopyranose in a condensed phase under super-acidic conditions (HF/SbF_5 .) However, most glycosylation reactions are carried out under milder conditions than those used in this elegant study and thus, an S_N2 -like or S_N2 mechanism can not be completely dismissed.^[5b] Ultimately, whichever pathway the coupling reactions follows will depend on the type of glycosylation.



Scheme 1. General mechanism of glycosylation with a non-participating group at C-2 (Only S_N1 mechanism shown).

In general, traditional reaction conditions are often harsh, which result in reduced chemo-, stereo- and sometimes also regiocontrol, particularly as chemical complexity in the substrates increases. Careful manipulations of protecting groups must be undertaken to control the regioselectivity and tune the reactivity of both glycosyl donor and glycosyl acceptor. In addition the promoter/activator, solvent, reaction temperature and

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concentration of reagents must be optimized in order to attain high levels of reactivity and selectivity.

The use of carefully selected organic molecules to catalyze challenging transformations in many branches of synthetic chemistry has already been demonstrated leading to expedient routes to compounds of interest, with high regio-, chemo- and enantioselectivity.^[7] Furthermore, organocatalysis offers a green and mild route to target molecules without requiring the use of harsh reagents or expensive transition metals as catalysts, thus bypassing the potential toxicity, expense and environmental issues inherent with traditional approaches.^[8] The last decade has seen an emergence of organocatalysis applied to carbohydrate synthesis, including applications in stereoselective glycosylation reactions as well as regio-selective protecting group manipulations. The methods are mild, high yielding and semi-orthogonal to other chemical strategies available, which allows for efficient access to oligosaccharide targets.^[9]

Organocatalytic glycosylations can be grouped into three main categories based on the type of catalyst used: Brønsted acids, thioureas and organoboron promoters. Although as chemists continue to explore the available chemical space, other classes of catalysts are now emerging. This microreview aims to highlight the most representative examples of organocatalysis applied to the glycosylation chemistry of the last 7 years including new emerging methodologies for organocatalytic glycosylation.

Enantioselective Brønsted acid catalysis by both chiral and achiral acids is a well established branch within organocatalysis.^[10] Brønsted acid catalysts offer a number of significant advantages over their more traditional Lewis acid counterparts. These catalysts are generally air and moisture stable over long periods of time and tend to be more environmentally benign, whilst also being suitable to scale-up. For these reasons, the use of Brønsted acids as glycosylation promoters has become very promising. While regio- and chemoselectivity can be controlled by the choice of protecting/leaving groups in the chosen building blocks; it has been long acknowledged that the stereoselectivity in a glycosylation reaction is dependent upon several factors, of which the intricate asymmetric relationship between the organocatalyst, glycosyl donor and acceptor is an important one. Thus, considerable effort in recent years has been devoted to the discovery of Brønsted acid catalysts that can effect stereoselective glycosylation, whilst controlling the regio- and chemoselectivity.

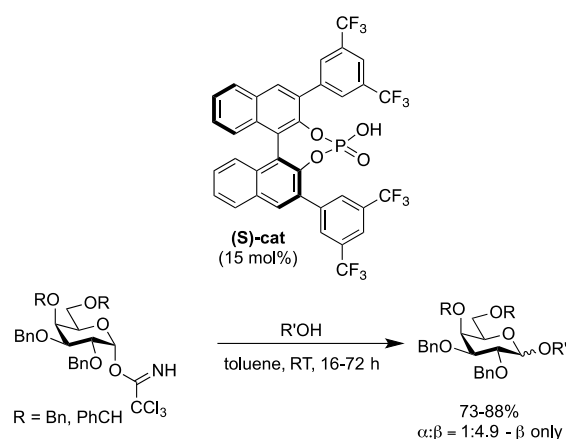
To exemplify this, Fairbanks and co-workers reported in 2010, the first use of a chiral Brønsted acid for the activation of trichloroacetimidate glycosyl donors.^[11] The team was inspired by an earlier report by Toste *et al.*^[12] whereby a chiral BINOL-derived phosphoric acid was employed to activate trichloroacetimidate moieties in the formation of episulfonium ions. In their report, BINOL-derived (S)-cat was used to activate α -galactosyl trichloroacetimidate donors to afford β -selective glycosides preferentially (**Scheme 2**). The high yielding reaction proceeds at room temperature over 16–72 hours and with moderate to excellent anomeric β -selectivity. Although the number of examples showcased is modest, using enantiomeric (R)-acid as

the glycosylation catalyst was detrimental to the β -stereoselectivity of the reaction, while reaction rate and yield remained the same. This suggested that the stereochemical outcome of the reaction was dependent on the chirality of the catalyst.

Ryan Williams received his Master of Chemistry degree from Durham University in 2015. He then moved on to doctoral studies at the University of Bristol, under the supervision of Dr. M. Carmen Galan. His research project involves the exploration of catalytic glycosylation methods.

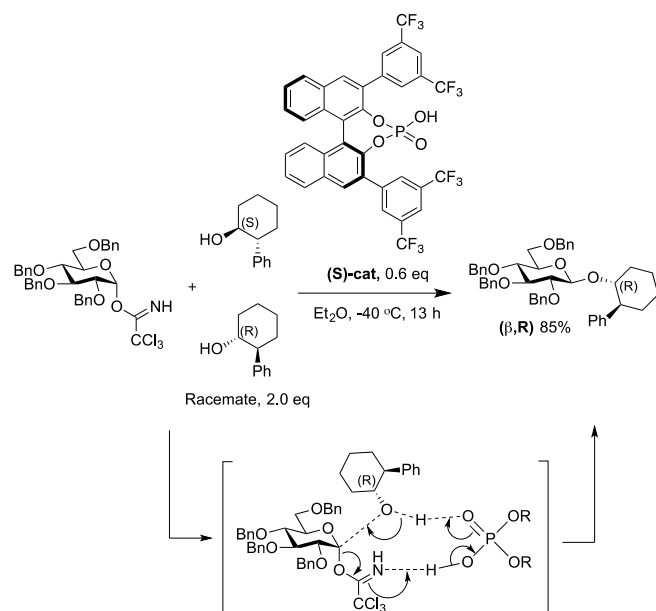


M. Carmen Galan is currently a Professor in Organic and Biological Chemistry at the School of Chemistry, University of Bristol (from August 2017). She received her Ph.D. in Organic Chemistry from the Complex Carbohydrate Research Center at The University of Georgia, USA, under the supervision of Prof. Geert-Jan Boons. She then moved to California to pursue post-doctoral research with Prof. Chi-Huey Wong at The Scripps Research Institute. After that, she continued her post-doctoral training at M.I.T with Prof. Sarah O'Connor. Carmen moved to the UK in October 2006 on a lectureship at the Organic and Biological Chemistry Department in Bristol. In 2008 she became a Royal Society Dorothy Hodgkin Fellowship and from 2012 she holds a five-year EPSRC Career Acceleration Fellowship. She is also the recipient of an ERC consolidator award.



Scheme 2. The chiral phosphoric acid-catalyzed glycosylation reported by Fairbanks and co-workers.

Expanding on the use of BINOL-derived phosphoric acids, Toshima and co-workers^[13] reported in 2013 the use of (S)-cat as a chiral Brønsted acid catalyst in α,β -stereo- and diastereo-selective glycosylation with glucosyl trichloroacetimidates. Exploiting the matched chirality between the chiral phosphoric acid, benzyl-protected glucosyl donor and the chiral OH-acceptors, the team were able to tune the reaction conditions to control the selectivity of the reaction exquisitely and obtain only the β -R-glycoside product. Typical reactions involve the coupling between an α -trichloroacetimidate glucosyl donor and a racemic mixture of secondary alcohols (R) and (S) in the presence of the (S)-cat, which under optimized conditions, afforded the corresponding (β ,R)-glycoside product in 85% yield as the sole product (**Scheme 3**). This selectivity for both a single diastereomeric alcohol and for the formation of a single anomeric product was successfully reproduced for other racemic mixtures of secondary alcohols. In all cases, total β -selectivity was achieved as well as a strong preference for the (R)-enantiomer. The authors proposed that while an (S)-cat-mediated S_N2 reaction mechanism can help explain the high β -stereoselectivity, the mechanism for the high diastereoselectivity is still unclear and that it might be attributed to the higher stability of the transient oxonium cation/(S)-cat/R-alcohol intermediate. Furthermore, the synthetic methodology was also applied to the preparation of a flavan glycoside natural product. Following preliminary mechanistic studies, the authors tentatively proposed a plausible mechanism for this transformation in which phosphoric acid (S)-cat is thought to act as a proton relay between the glycosyl donor and incoming alcohol, encouraging an S_N2 -type substitution.



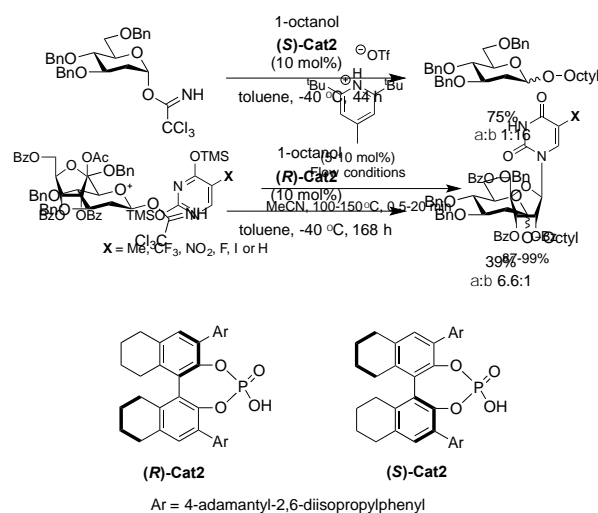
Scheme 3. Glycosylation of α -glucosyl trichloroacetimidate donors by a single enantiomer from a racemic mixture of alcohols, catalyzed by (S)-cat.

In 2014, Bennett and co-workers also described the use of chiral BINOL-derived phosphoric acids in glycosylations involving α - or β -trichloroacetimidate 2-deoxyglycosyl donors and 1-octanol

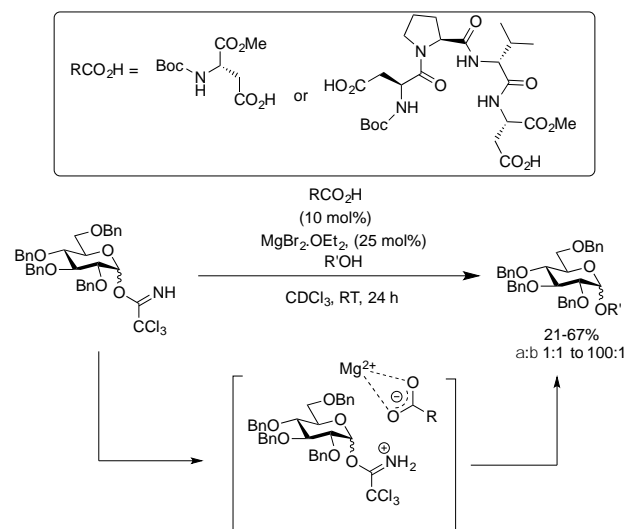
to prepare 2-deoxyglycosides. Deoxyglycosides are saccharides in which one (often at C-2) or several of the hydroxyl groups at positions around the sugar ring are replaced with a hydrogen atom. These glycosides are frequent features in biologically active natural products^[14] and drug compounds, including the calicheamicin and enediyne antibiotics and the anthracycline and apoptolidin anticancer drugs.^[15] Research into the biological underpinnings of deoxyglycoside containing compounds often reveals the carbohydrate component to be integral to the bioactivity of the compound. The synthesis of oligosaccharides bearing deoxyglycosides remains a challenge owing to their instability with respect to hydrolysis and the lack of a directing group at C-2 that may influence the stereochemical outcome of glycosylation.

The team were able to selectively bias the stereo-outcome of the reaction depending upon the matched/mismatched relationship between the chiral catalyst and anomeric configuration of the leaving group in the donor. It was found for example that by using sterically demanding chiral Brønsted acid catalyst (S)-Cat2 and an α -trichloroacetimidate donor, high levels of selectivity (1:16 α : β) could be achieved, while the same glycosyl donors with (R)-Cat2 required longer reaction times and gave lower selectivities. On the other hand, the glycosylation of β -trichloroacetimidate donor catalyzed by (R)-Cat2 afforded a significant enrichment of the α -anomer (6.6:1 α : β) (**Scheme 4**).^[16] Although the study is only carried out using perbenzylated glycosyl donors and a simple primary alcohol as the nucleophile, the results highlight the importance of matching the chirality of the glycosyl donor with that of the chiral Brønsted acid.

Scheme 4. Matched/mismatched catalyst/substrate glycosylation to yield 2-deoxyglycosides.



Scheme 5. Ribonucleoside preparation under flow conditions catalyzed by a pyridinium-derived acid organocatalyst.



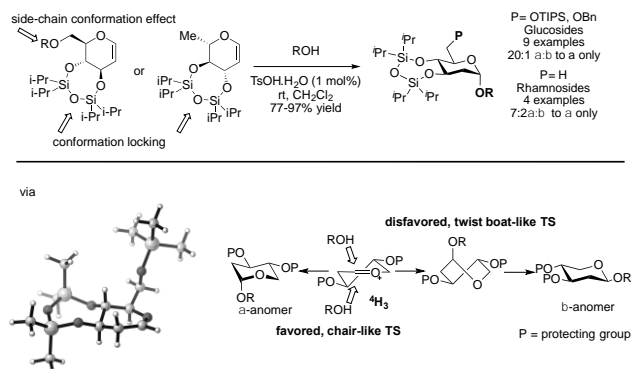
Scheme 6. Peptide-based Brønsted/Lewis acid dual catalysis glycosylation strategy.

Another area in which glycosylation becomes important is in the synthesis of nucleosides. Recently, Jamison and co-workers reported a Brønsted acid catalyzed glycosylation of a ribofuranose with various different nucleobases to produce ribonucleosides under flow conditions.^[17] Generally, ribonucleosides are synthesized via Vorbrüggen modification of the silyl-Hilbert-Johnson reaction. This approach requires stoichiometric activation by a Lewis acid e.g. trimethylsilyl triflate (TMSOTf), which leads to problems with functional group tolerance and generates high levels of chemical waste, particularly on preparative scale. By using 2,6-di-*tert*-butyl-4-methylpyridinium triflate as the organocatalyst, a protected ribofuranose bearing an anomeric acetate was *N*-glycosylated with various uracil, cytosine, guanine and adenine derived nucleobases (**Scheme 5**). The reaction proceeds in excellent yields and with complete β -selectivity, which can be attributed to the anchimeric assistance of the neighbouring benzoyl group at C-2. Catalyst screening experiments demonstrated that both the identity of the cation and the anion were paramount to obtaining high yields. The process works well in batch and also flow, as long as temperature is controlled to maintain reactant and product solubility, and also works under microwave irradiation conditions. The team also showed that the reaction could be scaled up in a commercially available flow system to produce multigram quantities of pure product with minimal optimization. Later work by the Jamison group used this glycosylation reaction as part of a telescoped flow multistep synthesis to prepare several 5'-deoxyribonucleoside pharmaceuticals.^[18]

The biomimetic emulation of enzyme-catalyzed glycosylation by using chemical reagents is an attractive goal in the chemical synthesis of oligosaccharides. Thus, Miller and co-workers sought to investigate the potential use of peptide-based carboxylic acids to facilitate stereoselective glycosidic bond formation.^[19] Initial studies, in which glucosyl trichloroacetimidate donors were reacted with cyclohexanol in the presence of a catalytic amount of various peptide-based carboxylic acids,

showed catalyst inhibition via formation of a glycosyl ester produced by reaction between the carboxylate anion in the peptide and the glycosyl donor. To overcome this obstacle, $\text{MgBr}_2\cdot\text{OEt}_2$ was added as a Lewis acid co-catalyst in combination with the Brønsted carboxylic acid. The authors proposed that the Mg^{2+} cation can coordinate with the carboxylate anion, allowing the activated glycosyl donor to undergo glycosylation reaction with the desired alcohol (**Scheme 6**). This approach was then used to prepare five glycosides using either N-Boc-protected aspartic (OMe) acid or N-Boc-protected tetrapeptide at room temperature over 24 hours. Products were synthesized in low to moderate conversions and a fair to excellent $\alpha:\beta$ ratio as determined by proton NMR, with a general preference for α -substitution. Despite the moderate yields and stereocontrol achieved via this method, this report represents an interesting application of amino acid-based carboxylic acids as glycosylation promoters.

Glycosylation reactions involving glucals as glycosyl donors tend to lack stereoselectivity and often lead to Ferrier rearrangement side-products.^[20] This is normally attributed to the lack of the C-4 OH as the axial substituent, which leads to the attack of the nucleophile from both faces of the ring.^[20b] It has been proposed that the acid-catalyzed direct nucleophilic substitution on a glycal is likely to proceed via oxocarbenium ion intermediates, which generally adopt two half-chair conformations ($^4\text{H}_3$ vs $^3\text{H}_4$), which upon nucleophilic addition lead to different diastereomeric products. The conformational equilibrium between the different species is influenced by steric effects as well as the electronic nature of the substituents.^[21] Galan, McGarrigle and co-workers hypothesized that protecting group induced conformational constraints on the charged glucal-derived oxocarbenium ion could be used to influence the stereoselectivity of the glycosylation. To that end, in 2014 the team reported a practical and efficient direct glycosylation protocol for the preparation of α -linked deoxyglucosides with high selectivity and yields using commercial tosic acid ($\text{TsOH}\cdot\text{H}_2\text{O}$) (1 mol%) as the Brønsted acid catalyst.^[22] In this instance, the stereocontrol during the reaction is controlled by the presence of a trans-fused cyclic 3,4-O-disiloxane protecting group in the glycal donor that locks the intermediate oxocarbenium cation that is formed during the reaction, in a conformation in which the C6-OSiR₃ group adopts a *gauche-gauche* conformation with respect to the endocyclic oxygen and C-4, which orientates the C6-O bond approximately parallel to the pseudo-axial substituents, favoring an axial attack from the nucleophile (**Scheme 7**). Reactions with glucal substrates gave products with higher stereocontrol than rhamnals, which was attributed to the conformational preference of the C6-side-chain,^[23] which is lacking in the rhamnal moieties. This report further highlights the importance of considering the effect that protecting groups have on the conformation of putative reaction intermediates and how these can be used to achieve stereocontrol.

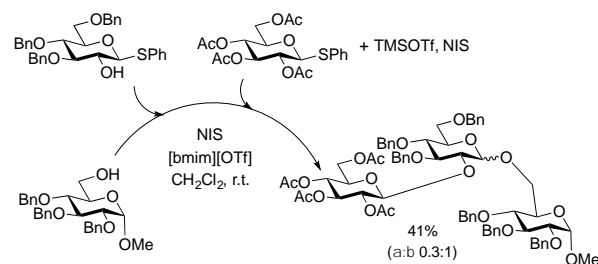


Scheme 7. Stereoselective glycosylations with trans-fused cyclic 3,4-O-disiloxane protected glucals.

2. Lewis Acid-Catalyzed Glycosylations

Lewis acid catalysis is perhaps one of the most common modes of activation in glycoside-forming reactions and has been the subject of several recent reviews.^[24] Most methods available rely on traditional approaches in which glycosyl bromides, glycosyl trichloroacetimidates, thioglycosides or glycosyl fluorides are used as donors that can be activated with standard Lewis acids (e.g. SnCl_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, AgOTf , ZnCl_2 or TMSOTf); whilst the presence of a C-2 participating group is used to direct the nucleophilic attack. Within this section, we aim to highlight the most unusual Lewis acid organocatalyzed reactions recently developed.

Orthogonal glycosylation protocols, whereby one glycosyl donor can be selectively activated in the presence of another donor, are highly desirable as a more efficient alternative to traditional approaches, which often require additional protection and deprotection steps and give low overall yields.^[25] Ionic liquids (ILs) offer an interesting alternative to traditional reagents in organic synthesis, including recent applications in the area of oligosaccharide synthesis.^[26] In this context, Galan and co-workers reported the first application of $[\text{bmim}][\text{OTf}]$ as a mild and versatile IL co-solvent and recyclable promoter for the room temperature glycosylation of both thiophenyl and trichloroacetimidate glycoside donors.^[27] The conditions are mild, and compatible with a range of hydroxyl and amino protecting groups, such as acetates, benzyl ethers, acetals, phthalimido (Phth) and trichloroethoxycarbonyl (Troc). Initial mechanistic studies suggested that $[\text{bmim}][\text{OTf}]$ can facilitate glycosylation reactions by the slow release of catalytic amounts of triflic acid and that the IL also protects the newly formed glycosidic linkage from hydrolysis.^[27-28] The triflated IL was capable of selectively promoting activated (armed) thiophenyl and trichloroacetimidate glycosyl donors in the presence of less active (disarmed) donors, which required the addition of catalytic triflic acid. The group were able to demonstrate the versatility of the IL/N-iodosuccinimide (NIS) promoter combination in a series of regio- and chemoselective reactivity-based one-pot glycosylation reactions at room temperature, where both donor and acceptor bear a free OH of distinct reactivity, to access branched and linear trisaccharides (**Scheme 8**).^[29]

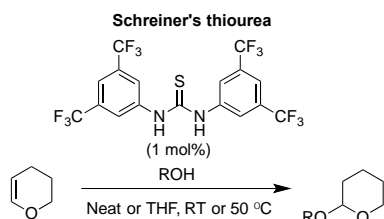


Scheme 8. IL-catalyzed one-pot reactivity based glycosylation.

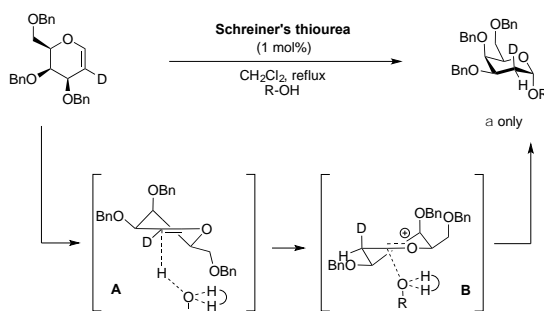
2. Thiourea Catalyzed Glycosylations

Thioureas have proven to be invaluable small-molecule catalysts for use in a plethora of chemical reactions.^[30] Taking inspiration from enzymatic active sites, organocatalytic thioureas have been designed to catalyze reactions through stabilization of the transition state by coordination of electron-deficient thiourea N-H protons to areas of (partial) negative charge. Thus, thioureas may act as dual hydrogen bond donors or as general weak acids. Complete mechanistic elucidation for these type of reactions has proven difficult to determine experimentally, as the degree of proton donation from the thiourea will depend on the substrate.^[31] Thioureas as organocatalysts offer several important advantages to alternative Brønsted or Lewis acidic catalysts. For many years Lewis acidic metals have been used to catalyze organic transformations, this is especially true in traditional glycosylation, in which heavy metal promoters including salts of silver and to a lesser extent tin and mercury have been commonly used.^[24] However, owing to the enthalpic drive towards metal coordination by heteroatoms, these metal catalysts are often highly sensitive to air and moisture, whilst also suffering from potential catalyst poisoning through binding to the product of the reaction. Thioureas are able to overcome these issues as they bind more weakly to the substrate, although this may come at the expense of catalytic turnover frequency.^[31] Conversely, strong Brønsted acids as catalysts are often employed in glycosylation reactions,^[7c] although deterioration of chemoselectivity through interaction with several functional groups on the substrates can often occur and the formation of side products due to the harsher conditions is also a potential problem. Thioureas as hydrogen bond donors/Brønsted acids are much weaker than traditional strong acid catalysts, imparting greater functional group tolerance, chemoselectivity and often better stereocontrol. These type of catalysts are also easily synthesized from commonly available building blocks and readily modifiable, as the groups linked to the N groups can be changed to attune the organocatalyst to the reaction, both by altering the electronic nature of the thiourea and by introducing chiral components, thus allowing stereochemical control to be administered. *N,N*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea or as it is commonly referred to, Schreiner's thiourea, has been shown to act as an efficient organocatalyst for a number of synthetically useful transformations.^[30e, 32] Of particular interest is the Schreiner's thiourea-catalyzed addition of alcohols to the enol

ether dihydropyran, which afforded the corresponding acetal over 15–24 hours using both aliphatic and aromatic alcohols. (**Scheme 9**).^[9b]



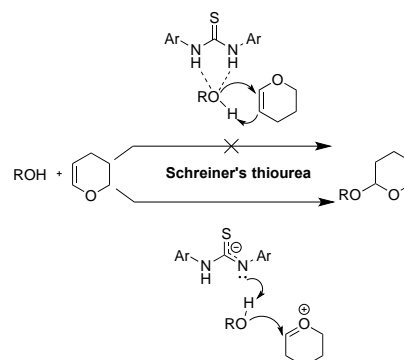
Scheme 9. Schreiner's thiourea-catalyzed acetal synthesis.



Scheme 10. Schreiner's thiourea-catalyzed glycosylation of galactals to furnish 2-deoxyglycosides.

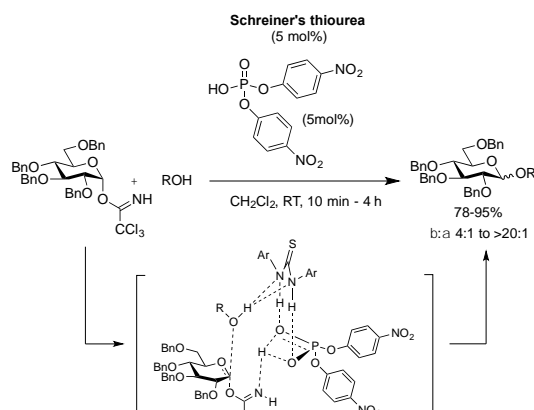
Taking inspiration from this work, in 2012, Galan, McGarrigle *et al.*^[33] reported the use of Schreiner's thiourea to catalyze the α -stereoselective synthesis of 2-deoxyglycosides from glycals.^[34] Using Schreiner's thiourea at low catalyst loadings (1 mol%), the team showed that the reaction is tolerant of a number of common protecting groups e.g. ethyl, allyl, benzyl, methoxymethyl ether (MOM) and silyl ether in both donor and acceptor, and proceeds smoothly with a wide range of primary and secondary OH acceptors, with excellent yields and complete α -selectivity in all cases. Mechanistic investigation of the reaction using deuterated galactal demonstrated that the newly formed bonds are *cis* to each other, suggesting a *syn* addition of the alcohol to the α face of the galactal (**Scheme 10**). The team rationalized that the reaction proceeds by formation of an alcohol–thiourea complex, which is able to deliver the proton selectively to the less hindered face of the galactal (A), followed by rapid collapse of the transient ion pair to give the product (B). It is hypothesized that the α anomer is formed preferentially during the C–O bond forming step due to favourable sterics, the electronic preference of the anomeric effect and a lower energy chair-like transition state. Furthermore, the method is semi-orthogonal to thioglycoside type glycosylations and to that end, the versatility of the approach was demonstrated in the one-pot synthesis of a trisaccharide, which was prepared in 58% yield with complete stereocontrol. It is important to highlight that the purity of the reagents and starting materials is of paramount importance for these types of thiourea catalyzed transformations, as small amounts of impurities can poison the catalyst.^[35]

Interestingly, recent work from Pápai and co-workers^[36] challenges the commonly held view that Schreiner's thiourea acts as a double-hydrogen bond donor in its organocatalytic capacity for the thiourea-catalyzed tetrahydropyranylation of alcohols. Instead, experimental and computational investigations by the group suggest that the thiourea acts as a Brønsted acid, protonating 3,4-dihydro-2H-pyran (DHP) to form an oxocarbenium ion, which then reacts with the alcohol (**Scheme 11**). The new proposed mechanism might also be relevant to the thiourea catalyzed glycosylations discussed in this Microreview.



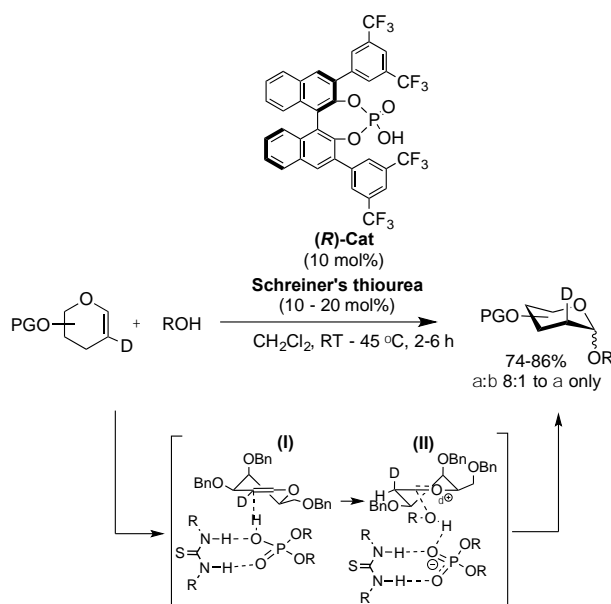
Scheme 11. Proposed thiourea-catalyzed tetrahydropyranylation of alcohols whereby a Brønsted acid (lower) pathway is favoured.

Various reports have shown that the combination of a Brønsted acid with a hydrogen bond donor (e.g. thiourea) can be used to enhance the catalytic activity of the acid and thus achieve increased yields, reaction rates and sometimes enantiocontrol.^[37] In light of this insight, in 2013, Schmidt and co-workers exploited the cooperativity between Schreiner's thiourea and an achiral Brønsted acid (bis(4-nitrophenyl) phosphate) to catalyze the glycosylation of suitably protected trichloroacetimidate glycosyl donors with a range of primary and secondary alcohols (**Scheme 12**).^[38] In their approach, a significant effect on reaction rate and yield and a moderate to excellent β -selectivity enhancement was achieved using this mild synergistic catalysis, which was dependent on the type of glycosyl donor and OH nucleophile. Four differentially protected glycosyl donors (galactose and glucose-type) were successfully subjected to the reaction conditions, including two bearing ester protecting groups at C-2 which may participate anchimerically during the glycosylation. As nucleophile acceptors, several alcohols including glycosyl alcohols were tested that bore alkynyl, alkenyl and aromatic functional groups. Mechanistic studies undertaken by the authors suggested an S_N2 -like transition state complex involving trichloroacetimidate donor, alcohol, and acid, in which the thiourea and acid complex functions as a proton transfer relay.



Scheme 12. Glycosylation of glycosyl trichloroacetimidate donors using thiourea-Brønsted acid cooperative catalysis.

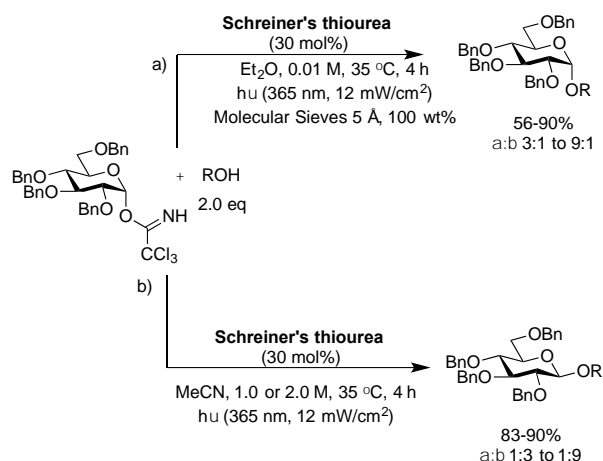
Another example of cooperative catalysis between a thiourea and a Brønsted acid was reported in 2017 by Galan and co-workers.^[39] The team had previously described the use of Schreiner's thiourea as a mild organocatalytic method for the preparation of 2-deoxygalactosides as described above. However, the mild reaction conditions meant that the catalyst was only efficient for the activation of galactal substrates and required long reaction times (24–48 hours).^[33] To address this issue, it was proposed that synergistic acid/thiourea activation could provide a more efficient and practical glycosylation strategy for the preparation of deoxyglycosides, compared to using a hydrogen-bonding organocatalyst or acid as the sole promoter. Furthermore, it was also hoped that by using a chiral acid, the stereoselectivity of the reaction could be further tuned. A series of BINOL-derived phosphoric acids, including an achiral phosphoric acid, were evaluated in the presence and absence of Schreiner's thiourea in model glycosylation reactions. The team found that (*R*)-3,3'-bis[3,5-bis(trifluoromethyl)phenyl]-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate ((*R*)-cat) in combination with Schreiner's thiourea could catalyze the reaction between suitably protected galactal, glucal and L-rhamnal donors and a range of OH nucleophiles, to yield the products in excellent yields and α -stereoselectivity (>30:1, α : β) and with shorter reaction times (2–6 hours) at either room temperature or 45 °C. It was also noted that while thiourea-induced acid amplification of the chiral acid via H-bonding is key for the enhancement in reaction rate and yield, the stereoselectivity of the reaction was highly dependent on the chirality of the acid. When the (*S*)-enantiomer of the acid, (*S*)-cat, was used in place of (*R*)-cat in the glycosylation reaction between benzyl protected galactal donor and a model glycoside acceptor, the α : β ratio of the product dropped from >30:1 to 7:1. Initial mechanistic investigations suggested a mechanism in which the acidity of (*R*)-cat is amplified by hydrogen bonding coordination of the thiourea. This thiourea-acid complex can then deliver a proton to the less sterically hindered α -face of the enol ether at C-2, leading to a short-lived oxocarbenium ion which is immediately trapped by the nucleophile, as shown in **Scheme 13**. The OH nucleophile is concomitantly activated by the phosphate intermediate that is generated in situ, which might help to explain the effect the chirality of the phosphoric acid has on the stereo-outcome of the glycosylation reaction.



Scheme 13. Glycosylation of glycals using thiourea/Brønsted acid cooperative catalysis.

The scope of applications of Schreiner's thiourea was further extended in 2016 by Toshima and co-workers to include photo-induced glycosylation reactions.^[40] Organophotoacids may exhibit increased acidity upon photoexcitation stimulated by exposure to ultraviolet (UV) radiation, enabling increased reactivity to be exploited.^[41] Toshima *et al.* had previously shown that a naphthol derived organophotoacid activator could be employed to promote the coupling between a glycosyl trichloroacetimidate and several alcohol nucleophiles, under photoirradiation. The reaction proceeded smoothly to give the corresponding glycosides in high yields with varying degrees of stereocontrol, which was substrate dependent.^[42] In an effort to find an organoacid that could help control the α / β -selectivity of the redox-type photoinduced glycosylation reaction, aryl thioureas were subsequently evaluated under long wavelength UV irradiation.^[40] The authors hypothesized that while an acid with a pKa of less than 5 is required to activate a glycosyl trichloroacetimidate donor and Schreiner's thiourea has a pKa of 8.5 in DMSO,^[43] under light irradiation at a 365 nm wavelength, the Brønsted acidity of the thiourea could be amplified. Indeed, this approach was shown to be viable and exemplified in the coupling reaction between a series of perbenzylated trichloroacetimidate glycosyl donors (glucose, galactose and mannose type) and a range of alcohol nucleophiles, producing glycosides in good to excellent yields and fair to good stereoselectivities (**Scheme 14**). Interestingly, the stereo-outcome of the glycosylation was found to be dependent on the concentration of the reaction. At high concentrations (1 or 2 M) β -selectivity was observed, even when the reaction was performed in solvents that generally favor α selectivity (e.g. Et₂O). Conversely, at low concentrations (0.005 to 0.05 M) α selectivity was observed. The authors attribute this effect to a changing reaction mechanism, as concentration changes. It is postulated

that in high concentration conditions, the reaction goes through an S_N2 type transition state, whereas at low concentration, an oxocarbenium ion is formed and then subsequently attacked by a glycosyl acceptor in an S_N1 type process. One of the advantages of the protocol is that the entire procedure requires minimal workup and the thiourea catalyst can be recovered and reused without loss in efficiency.

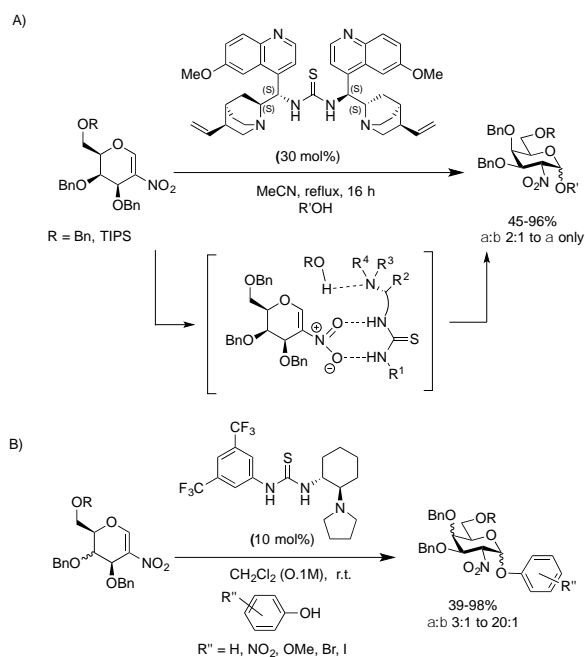


Scheme 14. The photoinduced glycosylation using Schreiner's thiourea developed by Toshima and co-workers. **a)** Low concentration conditions favouring the α anomer and **b)** high concentration conditions favouring the β anomer.

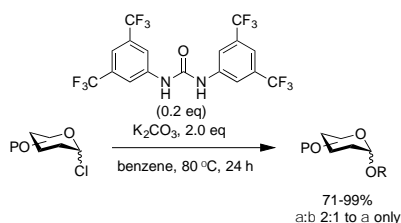
2-Amino-2-deoxyglycosides, often found as the *N*-acylated analogue, are structural motifs commonly found in oligosaccharides and glycoconjugates of biological significance.^[44] The stereoselective glycosylation of 1,2-*cis* aminoglycosides still remains troublesome since most amino protecting groups (e.g., amides, carbamates) tend to form 1,2-*trans*-type glycosides via neighboring group participation.^[45] In 2016, Galan and co-workers reported the stereoselective glycosylation of 2-nitroglactals catalyzed by a bifunctional thiourea organocatalyst.^[46] The group were inspired by the base-catalyzed 2-nitroglycal concatenation reaction,^[47] whereby anchimerically inactive 2-nitroglycosides, in which the nitro group acts as a masked amine/amide functionality, can be used as glycosyl donors. The team described the first application of a bifunctional cinchona/thiourea organocatalyst for the direct and α -stereoselective glycosylation of 2-nitroglactals to afford 2-amino-2-deoxygalactosides in moderate to excellent yields and α selectivity (**Scheme 15A**). The conditions are mild, practical, and applicable to a wide range of glycoside acceptors. It was proposed that while the thiourea functionality coordinates to the nitro group, and thus increases the electrophilicity of the nitroalkene, the pendant amine activates and directs the addition of the nucleophile into the prochiral alkene.^[48] In this way, the electrophilicity of the donor and the nucleophilicity of the alcohol are simultaneously enhanced, whilst the stereochemical configuration of the organocatalyst helps to direct glycosylation to the α -face of the donor. The applicability of the method is further exemplified in the synthesis of mucin-type Core 6 and 7 glycopeptides. Only a few weeks later, the group of Yoshida and

Takao also reported the application of a thiourea/pyrrolidine bifunctional organocatalyst for the highly α -selective organocatalytic glycosylation of 2-nitroglycals (galactal and glucal type) with phenol nucleophiles (**Scheme 15B**).^[49] The authors suggest, after initial mechanistic investigations, that the stereoselectivity of this reaction is kinetically controlled by the catalyst and that the chirality of the thiourea employed was key for the high α -selectivity observed. These results further demonstrate that in addition to solvent effects and the influence of the glycosyl donor and nucleophile acceptor, a chiral organocatalyst can be used to control the stereo-outcome of these glycosylation reactions.

Encouraged by some of the previously discussed thiourea-catalyzed glycosylation reactions, the Ye group sought to use a (thio)-urea to facilitate a Koenigs-Knorr glycosylation of glycosyl chlorides.^[50] It was thus determined that by using a urea catalyst in combination with additives, the desired disaccharides were isolated after 24 h at 80 °C in excellent yield and fair to complete α -selectivity for most glycosyl donors, unless a C-2 participating group was present, in which case β -selectivity was detected as expected (**Scheme 16**). In contrast to the complete α -selectivity seen for most glycosyl donors, when perbenzylated glucosyl donors were employed, poor α/β stereoselectivities were observed ranging from 2:1 to 3.3:1. To overcome this obstacle, the addition of tri-(2,4,6-trimethoxyphenyl)-phosphine was shown to aid high α -selectivity in the reaction and the challenging glycosyl donors could be synthesized in yields of 70-95% and improved α/β ratio (8:1 to 20:1). Preliminary mechanistic experiments suggest a urea-mediated hydrogen bond activation followed by subsequent glycosylation. Awaiting further mechanistic investigations, the authors proposed an explanation for the high levels of α -stereocontrol, on the basis of a non-covalent electronic interaction with the β -face of the anomeric carbon of the glycosyl donor, which directs the attack of the nucleophile to the α -face.



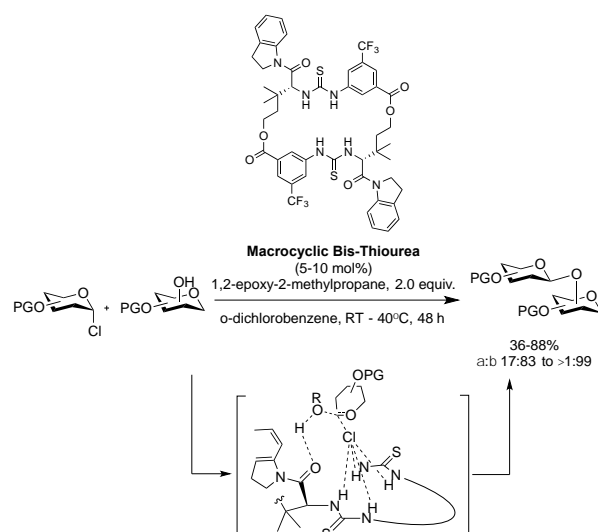
Scheme 15. Glycosylation of 2-nitroglycals using bifunctional organocatalysts.



Scheme 16. Urea-catalyzed Koenigs-Knorr glycosylation.

Macrocyclic bis-thioureas have been recently shown to catalyze stereospecific glycosylation reactions. Jacobsen and co-workers described in 2017, the very elegant organocatalytic activation of glycosyl chlorides by a novel chiral macrocyclic (*R,R*)-bis-thiourea^[51] (**Scheme 17**). The reaction follows a stereospecific invertive substitution pathway which is consistent with a cooperative mechanism, in which the electrophile and nucleophile are simultaneously activated to effect the stereospecific substitution reaction. The reaction is exemplified in the synthesis of *trans*-1,2-, *cis*-1,2-, and 2-deoxy- β -glycosides. Reactions generally take 48 h at room temperature or 40 °C and yield the desired disaccharide in good to excellent yields (62 - 88% yield) and β -stereocontrol. The donor scope of the reaction is significantly general, as 12 different glycosyl donors (e.g. glucose, galactose, mannose and a number of deoxyglycosides such as 2-deoxyglucose, L-rhamnose, L-fucose, D-xylose and 2-deoxy-aminoglycosides) were demonstrated to be amenable to the reaction conditions. This was exploited to prepare challenging 1,2-*cis* mannosides and 2-deoxy β -glycosides. Remarkably, the stereocontrol of the reaction is shown to depend almost entirely

on the configuration of the electrophilic glycosyl donor. Experiments devoted to independently alter the chirality of both the catalyst and the alcohol acceptor produced only very minor changes in the β -selectivity of the reaction, which is indicative of an S_N2 -type glycosylation. Furthermore, small changes in, for example, linker length or type of amide was detrimental to yield and diastereoselectivity, demonstrating that the macrocyclic *R,R*-bis-thiourea is finely attuned to allow the reaction to occur. The authors propose a transition state structure that occurs from simultaneous hydrogen bond activation of the reacting partners that encourages an S_N2 type substitution to occur. This mode of activation is reminiscent of the mechanisms employed by glycan processing enzymes.



Scheme 17. Glycosylation of glycosyl chlorides using a macrocyclic bis-thiourea organocatalyst.

There is no doubt that thioureas have become, and will continue to be, invaluable tools as organocatalytic glycosylation activators. Thus far, these mild reagents have proven to be useful in stereoselective transformations involving a variety of glycosyl donors and acceptors. Moreover, their catalytic utility and scope can be further expanded as glycosylation promoters by combining these small-molecule organocatalysts with other reagents (e.g. cooperative catalysis with Brønsted acids) or strategies (e. g. photochemistry).

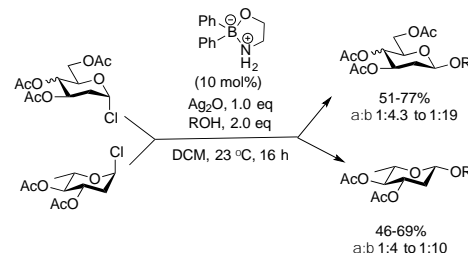
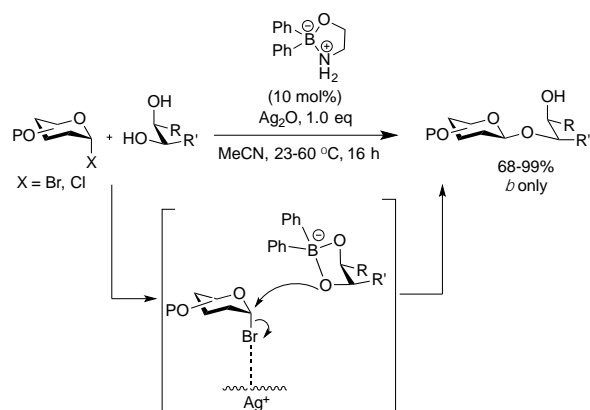
4. Organoboron Catalyzed Glycosylations

The use of organoboron derivatives as organocatalysts is an exciting field.^[52] Whilst the use of boron compounds as transmetallating agents in numerous transition metal-catalyzed processes is well documented, organoboron catalysis is comparatively underexplored. Trivalent boron possesses catalytically useful Lewis acidic electronics and exhibits a propensity to reversibly form boron-carbon and boron-oxygen bonds. Furthermore, there is extensive literature on the molecular recognition of carbohydrates by organoboron derivatives through

binding to *cis*-1,2 diol groups in a tetracoordinate manner.^[53] Harnessing these properties in a synthetically useful context makes organoboron catalysis a valuable addition to the organocatalytic glycosylation toolbox.^[54]

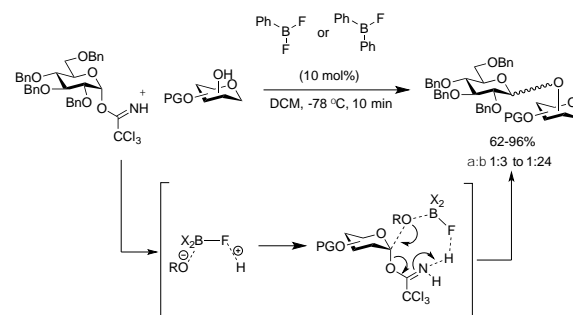
An elegant example of the application of organoboron compounds in Koenigs-Knorr glycosylation chemistry was reported in 2011 by Taylor and co-workers.^[55] Remarkably, the reaction uses a diphenylborinic acid-derived catalyst in the presence of stoichiometric silver(I) oxide to activate glycosyl acceptors that only require protecting groups at C-1 and C-6. Taking advantage of the presence of a 1,2-*cis* diol moiety in the acceptor, complete regioselectivity for the equatorial hydroxyl group within the *cis*-diol is achieved (**Scheme 18**). A series of glycosyl donors bearing acyl, benzyl and pivaloyl protecting groups were successfully glycosylated with a number of glycosyl acceptors including manno-, galacto-, fuco-, arabino- and rhamnosides in good yields and complete β -stereocontrol. Mechanistic studies suggest that diphenyl borinate esters activate 1,2-*cis*-diols towards electrophilic attack at the equatorial oxygen, similarly to organotin reagents.^[56] Furthermore, the anomeric configuration is not controlled by the catalyst, but is determined by the configuration of the glycosyl halide which reacts through an S_N2 -like inversion. Unlike most other glycosylation reactions this method does not require the strict use of anhydrous conditions; combined with the low toxicity and easy removal of the catalyst, it offers a valuable addition to oligosaccharide synthesis strategies. This methodology was later successfully applied to the regioselective glycosylation of the cardiac glycoside natural product digitoxin.^[57] More recently, in 2014, the Taylor group extended their use of the organoboron catalyst to the preparation of 2-deoxy- and 2,6-dideoxyglycosides.^[58] By using electron withdrawing acyl protecting groups on 2-deoxy glycosyl donors bearing an anomeric α -chloride leaving group, regioselectivity could be maintained at high levels, whilst β -selectivity was still strongly favored. Using this approach, three different glucosyl, galactosyl or rhamnosyl derived donors were successfully employed in the reaction with either 1,2- or 1,3-*cis* diol-bearing saccharide acceptors (**Scheme 19**).

Scheme 18. Regioselective glycosylation using diphenylborinic-derived acid.



Scheme 19. Regioselective synthesis of 2-deoxy and 2,6-dideoxyglycosides using diphenylborinic-derived acid.

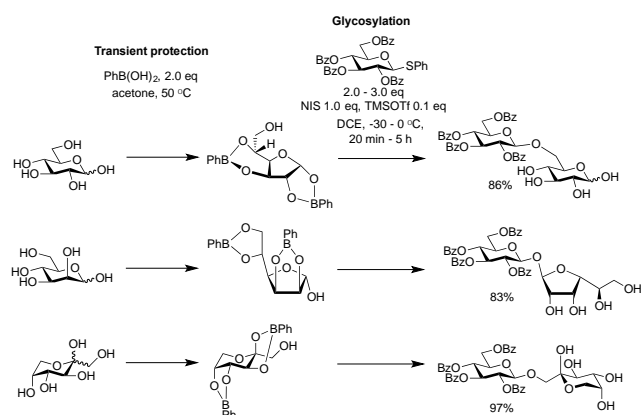
Schmidt and co-workers have also contributed to this area and in 2011, the group reported the use of phenylborondifluoride and diphenylboronfluoride as organocatalysts in the glycosylation of glycosyl trichloroacetimidate donors.^[59] The reported work arose from a desire to discover an activator that would only activate the glycosyl donor in the presence of the glycosyl acceptor, since trichloroacetimidate donors are rather labile under traditional activation methods, whereby degradation of the donor occurs (**Scheme 20**). The authors proposed that activation of the acceptor by the organoboron catalyst generates a boronate intermediate, which in turn activates the glycosyl donor through hydrogen bonding interactions followed by proton transfer, leading to glycoside formation. The reaction was exemplified in glycosylation reactions involving glycosyl trichloroacetimidate donors (glucose and galactose type) with several primary and secondary OH glycoside acceptors to yield the products within short reaction times in good-to-excellent yields and useful β -selectivities, which were superior to those observed when more traditional $BF_3 \cdot OEt_2$ is used. Based on their results, the authors suggest that the reaction might favour an S_N2 -type pathway.



Scheme 20. Glycosylation of trichloroacetimidate donors using phenylboronfluoride derivatives.

Another interesting application of organoboron reagents comes from the group of Nishino and co-workers, who in 2014 developed a regioselective glycosylation of fully unprotected carbohydrates via thermodynamically controlled bis(boronate) intermediates.^[60] By capitalizing on the propensity for boronic acids to bind to 1,2- or 1,3-*cis* diol moieties, fully unprotected sugars can be transformed into bis(boronate) intermediates in situ, leaving only one free hydroxyl group available for glycosylation with a suitably protected glycosyl donor. In this way,

whilst the bis(boronate) intermediates are not sufficiently stable to be stored for lengthy periods, they can be used as a “transient masking” protecting group strategy. Depending on the type of monosaccharide acceptor employed, different boronate-type substitution patterns are observed and hence a different hydroxyl group is left free for glycosylation (**Scheme 21**). In this manner, reaction of the bis(boronate) intermediates with thioglycoside glycosyl donors in the presence of *N*-iodosuccinimide and TMSOTf facilitates glycosylation with excellent yields and regio- and stereoselectivity. The latter is achieved via neighbouring group participation, induced by the presence of an ester at C-2 of the glycosyl donor. This atom economic approach represents an interesting alternative to current methods that rely on protection/deprotection schemes for the orthogonal protection of glycoside acceptors for glycosylation.

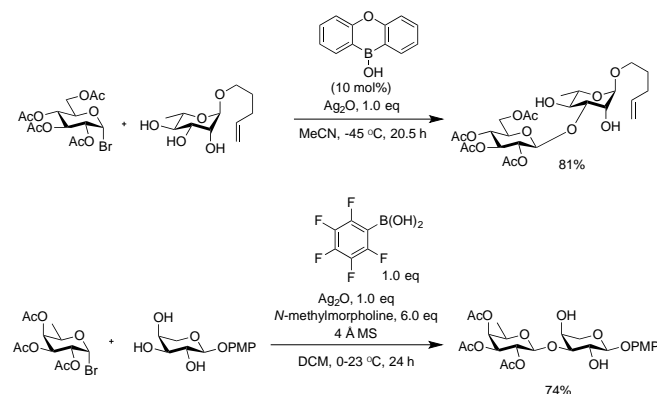


Scheme 21. Glycosylation of unprotected sugars via bis(boronate) intermediates.

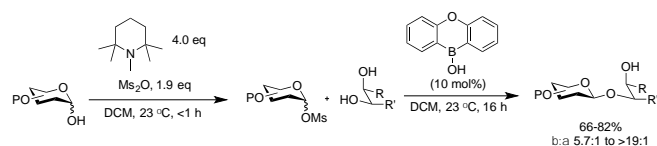
Since the initial application of organoboron reagents to oligosaccharide synthesis, other boron-based reagents with improved catalytic activity have also been described. In that respect, Taylor and co-workers reported the use of two different organoboron precatalysts that facilitated efficient glycosylations involving bromo glycosides in cases where their previously reported diphenylborinic acid-derived catalyst^[55] gave poor yields and/or regioselectivity.^[61] During work towards the total synthesis of a saponin-derived pentasaccharide natural product, the team demonstrated the utility of oxaboreaanthracene-derived borinic acid as a more reactive catalyst to effect the low temperature glycosylation reaction between a peracetylated α -bromo glucosyl donor and a rhamnoside acceptor with improved yields and regiocontrol, furnishing the desired product in 81% yield (**Scheme 22**). They also demonstrated that the choice of boronic acid and Lewis base is key in cases where matching/mismatching of glycosyl donor configuration adversely affects the regioselectivity of the glycosylation. This was exemplified in the successful synthesis of β -(1 \rightarrow 3)-D-Fuc-L-Ara disaccharide, whereby the combination of pentafluorophenylboronic acid and *N*-methylmorpholine afforded the product in 74% yield. This report further validates that catalyst- or reagent-controlled glycosylations as initial OH differentiation steps, followed by substrate-controlled transformations of the

resulting disaccharides are promising strategies that could be applied to the synthesis of other important oligosaccharide targets.

More recently, the same group further expanded the scope of the oxaboreaanthracene-derived borinic acid catalyst to the glycosylation of glycosyl mesylate donors.^[62] It was discovered that glycosyl mesylates, prepared in situ from the reaction between a glycosyl hemiacetal and methanesulfonic anhydride within one hour at room temperature, serve well as substrates in the organoboron-catalyzed glycosylation. As previously reported, 1,2- or 1,3-*cis* diols were used as glycosyl acceptors, and reactions proceeded well with a regioselective preference for the equatorial hydroxyl group on the saccharide acceptor. Disaccharides were obtained over 16 h in high yields and with good to excellent β -selectivity at room temperature in most cases (**Scheme 23**). Interestingly, reactions carried out in the absence of the organoboron catalyst afforded the products with modest to high α -selectivity, demonstrating the stereochemical influence exerted by the organocatalyst. Extensive mechanistic and kinetic studies undertaken provide evidence for an associative mechanism in which an intermediate boronic ester formed through reaction of the diarylborinic acid and the glycosyl acceptor undergoes glycosylation with the more reactive α anomer of the glycosyl mesylate favouring β -linked products.



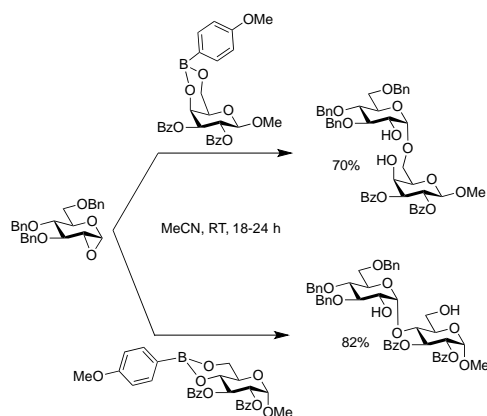
Scheme 22. Choice of Lewis base and/or organoboron catalyst is important to facilitate challenging glycosylations.



Scheme 23. In situ formation of glycosyl mesylate donors and subsequent glycosylation using a diarylorganoboron catalyst.

The ability to synthesize 1,2-*cis* glycosides efficiently by catalyst-controlled methods is a very challenging task. In 2015, Toshima, Takahashi and co-workers reported a boronic ester catalyzed glycosylation that is able to facilitate the formation of glycosidic linkages with excellent regiocontrol and 1,2-*cis*- α -stereoselectivity.^[63] The team developed a very elegant strategy in which 4-methoxyphenylboronic acid reacts reversibly with a 1,2- or 1,3-*cis* diol glycosyl acceptor to form the corresponding

boronic ester. The boronic ester is then able to activate 1α - 2α -anhydro glycosyl donors in acetonitrile and produce oligosaccharides in high yield with excellent regio- and stereoselectivity (**Scheme 24**). The authors provide a mechanistic rationale for the observed regio- and stereoselectivity by considering the geometries of the possible competing transition states that are formed by the interaction between the glycosyl donor and the boronic ester-activated glycosyl acceptor. Steric hindrance of the aromatic ring with the anomeric proton is thought to be a key factor in influencing which transition state is preferred and hence whether 1,6 or 1,4 regioselectivity is obtained. Thus, when a 1α - 2α -anhydro glucoside donor is used with 4,6-dihydroxylated galactosyl acceptor, the α -1,6-glycoside product is made; whereas when glucosyl acceptor is used under the same conditions, the α -1,4-linkage is obtained. Overall, the reaction conditions are mild and practical and work well in range of glycosyl donors and acceptors bearing common protecting groups. Furthermore, the authors exemplified the versatility of the method by synthesizing a naturally occurring isoflavone glycoside.



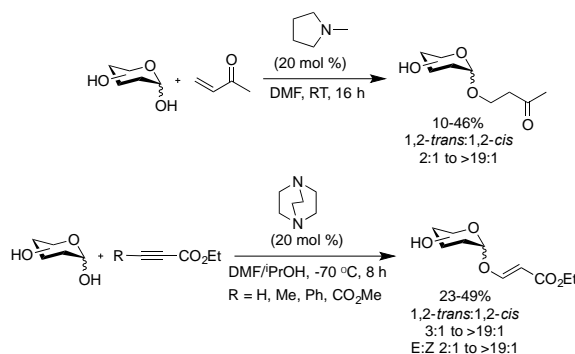
Scheme 24. Organoboron-catalyzed synthesis of 1,2-*cis*-glycosides.

5. Organocatalytic Glycosylations of Unprotected and Unactivated Carbohydrates

Most glycosylation reactions are carried out using partially protected carbohydrate building blocks as a means to control the regioselectivity and reactivity of the reaction. Typically a leaving group is installed at the anomeric position of the glycosyl donor which can be activated to effect glycosylation in the presence of the chosen nucleophile. Fisher type glycosylation is one of the few examples where a direct glycosylation of unprotected and unactivated glycosides is described, however, those processes rely on the use of a strong acid catalyst, high temperatures and an excess of OH nucleophile, which is often the reaction solvent. In this context, Lewis acids have also been deployed in glycosylation reactions of unprotected carbohydrates, including examples where the reactions are performed in ionic liquids.^[64]

In the context of organocatalysis, Mahrwald *et al.* reported in 2013 the glycosylation of unprotected sugars using

triphenylphosphine and tetrabromomethane under neutral conditions.^[65] A series of unprotected monosaccharides (hexoses and D-ribose) were glycosylated with simple alcohols at room temperature. Glycoside products were obtained after 16 hours in low to excellent yields and with poor to good α/β stereoselectivity. Although mechanistic investigations weren't described, the authors report that under these reaction conditions, thermodynamic control of the glycosylation is observed and as a consequence, the formation of pyranosides is favoured. Following their initial report, in 2014 the same group described a novel and stereoselective organocatalyzed approach to access glycosides via base-catalyzed conjugate additions of unprotected and unactivated monosaccharides to activated alkenes or alkynes.^[66] The method employs a sub-stoichiometric amount of either *N*-methylpyrrolidine (NMP) or 1,4-diazabicyclo[2.2.2]octane (DABCO) as the organocatalyst. The reaction was exemplified in glycosylation reactions between a range of pentose and hexose saccharides with methyl vinyl ketone to produce the corresponding glycoside products in 10-46% yield and fair to excellent preference for the 1,2-*trans* substituted glycoside when using NMP as the base. Alkynes were also amenable to the reaction, as demonstrated with the glycosylation of ribose and xylose with internal and terminal alkynes in the presence of DABCO as the catalytic base. In this instance, the alkene products were isolated in low to fair yields and with all but one example having a >19:1 α/β anomeric ratio in favor of the 1,2-*trans* product (**Scheme 25**). It is proposed based on the experimental data that the final configuration of the anomeric carbon appears to be dictated by the configuration at C-2 of the starting material, thus the α -stereoselectivity observed could be justified on the basis of steric hindrance in combination with the anomeric effect. The authors further illustrate the potential of the strategy as a tool in total synthesis by performing a post-glycosylation Wittig reaction on an alkenyl glycoside.



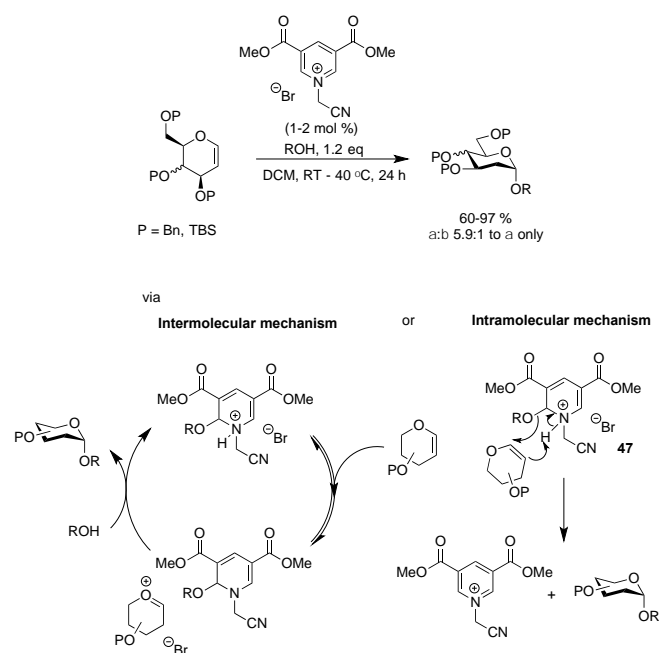
Scheme 25. Amine-catalyzed Michael addition of unprotected carbohydrates with alkenes and alkynes.

6. Other Organocatalyzed Glycosylations

Whilst many recent advances in organocatalytic glycosylations fall into one of the categories discussed before, as

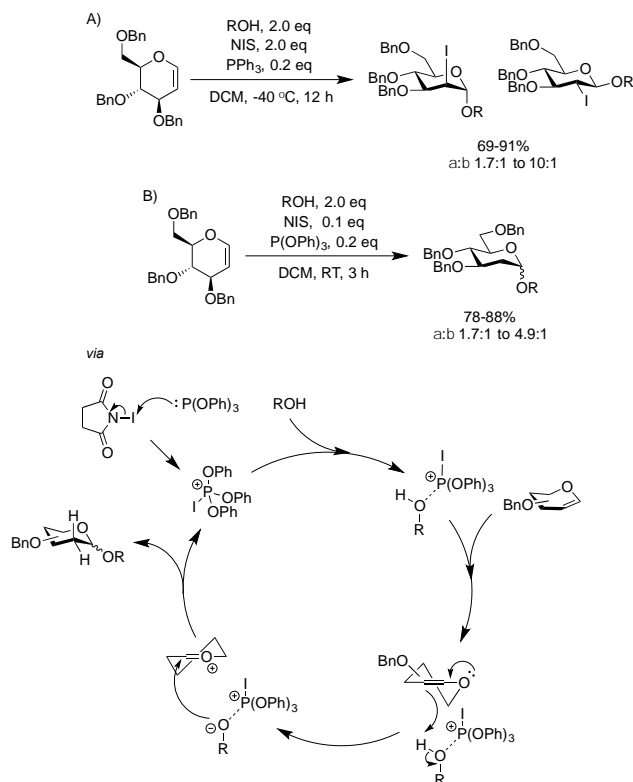
glyco-chemists continue to explore the organocatalysis chemical tool-box, a number of other approaches have emerged and those are covered in this section.

For example, Berkessel and co-workers recently reported the use of electron deficient pyridinium salts as catalysts to furnish 2-deoxyglycosides from glycals.^[67] After a screen of different pyridinium salts, it was found that 1-2 mol% of an electron-deficient diester pyridinium salt was the optimal catalyst for the glycosylation between glucals and galactals with a series of primary and secondary OH nucleophiles within 14 hours. The reaction was tolerant of most common protecting groups in both donor and acceptor in excellent yields and with complete α -stereocontrol (**Scheme 26**). Based on mechanistic investigations, the authors proposed two plausible mechanisms: an intermolecular process, whereby addition of the alcohol to the 2-position of the pyridinium salt to form a protonated hemiaminal is followed by acid catalyzed glycal activation, forming an oxocarbenium ion which is then captured by a second OH molecule to yield the glycoside product; alternatively an intramolecular mechanism in which proton transfer from the pyridinium cation followed by alcoholate transfer from the aminal in a concerted manner could not be ruled out.



Scheme 26. An electron deficient pyridinium salt as a glycosylation catalyst for the synthesis of 2-deoxyglycosides from glycals and the proposed mechanisms.

Another interesting approach developed by Toshima and co-workers in 2015 describes the use of *N*-iodosuccinimide (NIS) in combination with a phosphine to prepare both 2-deoxy-2-iodo-glycosides and 2-deoxyglycosides from glycals.^[68] Inspired by earlier work by the Ishihara team,^[69] the authors sought to develop an improved method for synthesizing 2-deoxy-2-iodo-glycosides that did not involve the use of strong Brønsted acids that may interfere with acid sensitive substrates.



Scheme 27. NIS/Phosphorus compounds-catalyzed synthesis of A) 2-deoxy-2-iodo-glycosides and B) 2-deoxyglycosides and proposed mechanism of glycosylation.

This goal was realized, and during the investigations it was also found that by selecting the appropriate phosphine, 2-deoxyglycosides could be synthesized efficiently. In order to generate 2-deoxy-2-iodo-glycosides, a combination of NIS and triphenylphosphine was employed at low temperature, with products obtained over 12 hours in excellent yield and good α / β stereocontrol (**Scheme 27**). A number of alcohols were screened with tri-*O*-benzyl-glucal, including several bearing acid sensitive groups such as acetals and silyl ethers. In these cases use of the triphenylphosphine additive in place of the more traditional triflic acid gave superior yields. Mechanistically, the reaction is thought to proceed via activation of the glycal by a reactive phosphonium iodide to give a glycosyl iodonium cation. This cation then undergoes nucleophilic addition of the alcohol to furnish the product and regenerate catalytically active triphenylphosphine. Interestingly, the use of triphenylphosphite in place of triphenylphosphine in the presence of catalytic amounts of NIS (0.1 equiv) at room temperature permits the construction of 2-deoxyglycosides in excellent yields and good stereocontrol. Initial mechanistic investigations with deuterated ROD nucleophiles lead to a proposed glycosylation mechanism, beginning with the formation of a phosphonium iodide, generated from the reaction between NIS and $P(OPh)_3$, which is able to accept electron density from the alcohol owing to the electron withdrawing effect of the phenoxy groups. The reacting glycal then abstracts the alcoholic proton to form an oxocarbenium ion,

which is then trapped by the generated alkoxide, furnishing the 2-deoxyglycoside product and regenerating the phosphonium iodide in an organocatalytic manner.

7. Conclusions and Outlook

Despite the many advances in the field, a general routine method for the stereoselective synthesis of all types of complex oligosaccharides has eluded us thus far. This big challenge is mostly due to the capricious nature of the glycosylation process, which is not only dependent on the reaction conditions (e.g., temperature, solvent, reagent concentration), but also dictated by the type of glycoside donor, acceptor nucleophile, and nature/chirality of the catalytic system.

This review highlights that as we gain a better molecular understanding of the glycosylation process, novel and improved catalytic systems and strategies can be developed. The application of organocatalysis to glycosylation chemistry, as a milder alternative to more traditional reagents, offers new opportunities in the field. As showcased in this review, new organocatalytic glycosylations that are able to effect the coupling reaction in an efficient manner, including examples where not only the stereoselectivity, but also the regioselectivity of the reaction can be controlled by the catalyst, have been developed. The potential for small-molecule biomimetic strategies in particular is tantalizing, as the successful imitation of the sublime chemical control seen in enzyme catalyzed glycosylations would be a great boon to the field. Thus, organocatalytic approaches to carbohydrate synthesis offer an invaluable addition to the glycoscientist's toolbox of methods towards the construction of complex natural and unnatural carbohydrate derivatives.

Research in organocatalysis for asymmetric synthesis has shown that these type of catalysts can be tuned to give optimum reactivity and control, whilst maintaining a diverse substrate scope. Therefore, looking forward, further adaptation of small molecule organocatalysts to suit the unique and formidable requirements of the glycosylation reaction with high control of chemo-, regio- and stereoselectivity is still necessary; and while a universal glycosylation catalyst might not be possible, we should be able to develop a set of catalysts to achieve all required glycosylations.

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Keywords: organocatalysis • glycosylation • carbohydrates • stereoselectivity • homogeneous catalysis

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